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Improved survival rates of AML patients following admission to the intensive care unit.

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Improved survival rates of AML patients following admission to the intensive care unit.

Original Report

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ABSTRACT

Induction chemotherapy in AML patients may have life-threatening side effects requiring intensive care unit (ICU) treatment. We analyzed all AML patients receiving intensive chemotherapy at a single academic center between 01/2006-12/2016. At least one ICU admission was observed in 32% (76/240) patients, and 33% of those died following ICU admission. Whereas the ICU admission proportion remained stable, mortality after ICU admission decreased from 14% (2006-2008) to 3% (2014-2016; P = .056). The number of failing organ systems inversely correlated with surviving ICU admission (P < .001). Sepsis and renal, cardiac and pulmonary failure were each associated with higher mortality. With increasing ICU duration, survival probability decreased (P < .001), but remained >50% even after 14 days of ICU treatment. Progression-free and overall survival were comparable between ICU surviving patients and patients never needing ICU support. In conclusion, outcome after ICU admission of AML patients has substantially improved in recent years.

INTRODUCTION

Intensive chemotherapy with curative intent is standard of care in fit patients with acute myeloid leukemia (AML). Inevitably, this treatment is associated with prolonged immunosuppression and impaired mucocutaneous barriers [1]. Consequently, such patients are prone to infections and frequently require intensive care unit (ICU) support. Previous studies reported that 15-28 % of AML patients need to be admitted to the ICU during induction chemotherapy [2,3], with respiratory failure being the most common indication for admission [4].

Traditionally high mortality rates underlie a restrictive attitude among intensivists to unplanned transfers of hemato-oncologic patients to the ICU [5]. However, perspectives for critically ill cancer patients have substantially improved in recent years and led, together with improved survival rates of patients admitted to general ICUs, to less reluctance to admit AML patients to the ICU [6-9]. Formerly, neutropenic AML patients who developed organ failure were considered to have a poor prognosis; however, the concept that neutropenia is predictive for ICU mortality has paved the way towards a more differentiated approach regarding ICU treatment of AML patients [10]. Accordingly, recent reports have indicated that the need for mechanical ventilation, multi-organ failure, invasive fungal infection, and high illness scores at ICU admission are factors associated with high mortality rates among AML patients [4,11].

In this study, we retrospectively reviewed the medical records of all AML patients receiving intensive chemotherapy at a single academic center between 01/2006 and 12/2016. We analyzed admission proportion to the ICU, assessed outcomes during the study period, and we tested variables associated with mortality in the ICU. Our data support the concept that outcomes of patients with AML after ICU admission have substantially improved in recent years.

METHODS

Patients

In this retrospective analysis, we investigated all consecutive patients with AML at first diagnosis or at relapse who received intensive chemotherapy with curative intent at the University Hospital of Bern, Switzerland between 01/2006 and 12/2016. Patients with palliative AML treatment or best supportive care were excluded from this analysis. Clinical characteristics of the patients are summarized in **Table 1**. This study was approved by the local ethics committee of Bern, Switzerland (decision number #1138/17).

Treatment

Patients were treated in or according to the SAKK/HOVON-42, -92, -102, -103, or -132 protocols. In induction cycle 1, patients received cytarabine 200 mg/m² on days 1-7 and idarubicin 12 mg/m² on days 1-3. In induction cycle 2, cytarabine 1000 mg/m²/q12h on days 1-6 and amsacrine 120 mg/m² on days 1-3 (until 2012) or daunorubicin 60 mg/m² on three days (since 2013) were given. For consolidation, patients underwent allogeneic hematopoietic stem cell transplantation, autologous transplantation or a third cycle of consolidation chemotherapy. Allogeneic transplantation was offered to poor-risk patients (with a sibling or an unrelated matched donor) and to intermediate-risk patients (with a sibling matched donor). The remaining patients preferentially received busulfan/cyclophosphamide high-dose chemotherapy and autologous stem cell transplantation or, alternatively, a third conventional chemotherapy cycle with etoposide and mitoxantrone. For relapsing patients, the CLAG-Ida regimen was given consisting of cladribine 5 mg/m² days 1-5, cytarabine 2000 mg/m² days 1-5 and idarubicin 8 mg/m² days 1-5 [12].

Starting 01/2012, routine antifungal prophylaxis with oral posaconazole was introduced to all patients thereafter. However, no routine antibiotic prophylaxis was applied. Patients received platelet and red cell transfusions when platelets fell below 10 G/L or if clinically indicated, and

hemoglobin was below 80 g/L, respectively. Patients were hospitalized for the entire procedure, and they were discharged after adequate hematologic recovery and physical reconditioning.

Definitions

Risk assessment was performed according to the European Leukemia Net (ELN) classification, and response criteria were applied according to the International Working Group criteria [30]. Bone marrow examination was scheduled on days 18 and 28 of each induction cycle, and after hematologic recovery following consolidation treatment. Morphologic complete remission (CR) was defined as bone marrow blasts below 5% together with neutrophil counts exceeding 1.0 G/L for three consecutive days and platelet counts above 100 G/L without transfusions in the three previous days [30]. Complete remission with incomplete hematologic recovery (CRi) was defined as bone marrow blasts below 5% with neutrophil counts below 1.0 G/L or platelet counts below 100 G/L.

Progression free survival was calculated from the date of achieving CR1 until disease progression, death or last follow-up (censored Dec 31, 2017), whichever occurred first. Non-relapsing patients were censored at the last date of follow up (censored Dec 31, 2017). Overall survival was calculated from the date of achieving CR1 until death or last follow-up. Patients still alive or lost to follow-up were censored at the last date when they were known to be alive.

Sepsis in this study was defined in a patient with an infection when two of the following four criteria were identified: temperature >38.0°C or <36.0°C; respiratory rate >20/min or $PaCO_2$ <32 mmHg (<4.3 kPa); heart rate > 90/min; and white blood cell (WBC) count >12 G/L, <3 G/L, or >10% immature neutrophils. SAPS II scores were determined and used according to the criteria defined in the European/North American Multicenter study [31]. Definitions of failing organ systems as used in this analysis are outlined in more detail in **supplementary Table S4**.

Statistical Analysis

Curves depicting progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared between patient groups using the log-rank test. We calculated hazard ratios using Cox regression analysis including ICU admission as time varying explanatory variable, patient age, ELN risk classification, antifungal prophylaxis, year of therapy onset and an interaction term of ICU admission and year as covariates to investigate whether the impact of ICU admission on the hazard remained the same over time. Proportional hazard assumptions were investigated. As only five patients had an undefined ELN risk, these were assigned to the best category in order to allow for ordered categories. We made a sensitivity analysis to check the effect of assigning these patients to the intermediate category and found the same results. Continuous data are presented as median and range, categorical variables as number and percentage, univariate comparisons were done using Fisher's or unpaired t-tests, respectively, and a value of $P < .05$ was considered significant. All CIs and reported *P* values are two-tailed, and the statistical analysis was performed using GraphPad Prism® Version 6.0 (GraphPad Software, La Jolla, CA) and Stata 14.2 (Stata Corporation, College Station, TX).

RESULTS

Patient characteristics

We analyzed 240 consecutive patients with AML receiving at least one cycle of intensive chemotherapy with curative intent at a single academic center (University Hospital Bern, Switzerland) between 01/2006 and 12/2016. Patients receiving palliative treatment or best supportive care were not included as were patients admitted to the ICU at first diagnosis before initiation of AML treatment. Clinical characteristics of the patients are summarized in **Table 1**. The median age was 57 years.

We found that 76 of these 240 (32%) AML patients had to be admitted at least once to the ICU during intensive chemotherapy. The median number of ICU admissions per patient was one (range one to three admissions), and the 76 patients had a total of 92 ICU admissions. All patients were admitted to the same tertiary medico-surgical ICU of the same institution in which AML treatment was performed. No significant differences in clinical characteristics at diagnosis of AML were observed (**Table 1** and **Supplementary Table S1**) between patients with and without ICU admission, and cytogenetic and molecular genetic abnormalities and ELN risk groups were equally balanced.

We found that 25 of the 76 (33%) patients needing ICU treatment died following ICU admission. The mortality rate of male patients admitted to the ICU was 40%, and it was 21% for female patients (P = .085). Again, no significant differences in clinical characteristics at diagnosis of AML were observed (**Table 1** and **Supplementary Table S1**) between AML patients with and without ICU admission, and cytogenetic subgroups and ELN risk groups were evenly distributed. Regarding the molecular mutation profiles, *NPM1* mutations were more common in the ICU survivor group (29%; 15/51 patients) compared to patients with fatal outcome after ICU admission (8%; 2/25 patients; P = .042).

ICU admissions during study period

The ICU admission rate of all AML patients remained unchanged during the study period with a median of 34% of all AML patients admitted at least once to the ICU during intensive AML treatment (**Figure 1**). Also, the SAPS II scores, median value at ICU admission for all patients was 63, did not change during the time periods of the study (**Figure 1**). Whereas 14% (10/74) of all AML patients being admitted to ICU died in the beginning of the study period (2006 to 2008), this mortality rate dropped to 3% (1/34 patients; P = .056) in the last study period (2015 to 2016). Thus, the probability of AML patients to survive ICU treatment increased significantly during the study period.

Factors predicting ICU outcome in AML patients

Most admissions to the ICU occurred during the first induction cycle (60%; 55/92 admissions). The mortality rate per ICU admission was similar for induction cycles 1 and 2 and for consolidation (between 20% and 27%), but was higher for relapsing patients receiving re-induction treatment (40%; 4/10; **Table 2**). ICU admission occurred at a median of 15 days (range 1 to 69) after start of chemotherapy and 11 days (range 1 to 62) after onset of neutropenia.

The median duration in the ICU was three days (range 1 to 38) in the ICU survivor group and six days (range 1 to 19) in the group with fatal outcome. The probability to survive decreased with increasing ICU duration ($P < .001$; **Figure 2**). The survival probability at the first day after ICU admission was 97%, and it steadily decreased to 68% if a patient spent 19 or more days in the ICU.

The following clinical conditions were associated with outcome after ICU admission: Patients who died during ICU admission had significantly more often a septic condition (92%; 23/25 patients compared to 64%; 43/67 patients; $P = .009$). Also renal failure (56%; 14/25 versus 30%; 20/67 patients; $P = .029$), pulmonary failure (96%; 24/25 versus 57%; 38/67; $P < .001$) and cardiac decompensation (92%; 23/25 versus 60%; 40/67 patients; $P = .002$) were more common in the group of patients who died following ICU admission. Patients with a fatal outcome after ICU admission had in more than 90% sepsis, cardiac and pulmonary failure together. Overall, a median of five (range 3 to 9) out of ten assessed failing organ systems were identified in patients dying during ICU treatment, whereas the ICU survivor group had a median of three (range 1 to 8) failing organ systems (**Table 2**). In general, the survival probability dropped ($P < .001$) with increasing number of failing organ systems, with a survival probability of only 50% with seven or more failing organ systems (**Figure 2**).

We also assessed the impact of the need for therapeutic modalities in the ICU on outcome. Mechanical ventilation was needed in 100% (25/25 patients) of all ICU admissions with lethal outcome compared to 43% (29/67 patients) in the ICU survivor group ($P < .001$). The need for catecholamine support (96%; 24/25 versus 36%; 24/67 patients; $P < .001$), dialysis (36%; 9/25 versus 9%; 6/67; $P = .004$) and for AED (automated external defibrillator; 16%; 4/25 versus

3%; 2/67; *P* = .044) was more common in the group with fatal outcome after ICU admission (**Table 2**).

Finally, **Table 3** presents the results of the multivariate analysis. The hazard of disease progression or death decreased by 11% per year (HR 0.89, CI 0.83 to 0.95, p<0.001), whereas ICU admission did not show an association with this outcome, neither was there an interaction of ICU admission and year of onset of therapy. The hazard of death decreased even by 16% per year (HR 0.84, CI 0.78 to 0.9, p<0.001), while survival after ICU admission did improve, but less than survival in patients who did not need to be admitted to ICU, as indicated by the significant interaction.

Infections and outcome after ICU admission

We found no differences in incidence and types of bacterial pathogens isolated in AML patients with fatal outcome compared with ICU surviving patients (**Supplementary Table S2**). Bacterial pathogens were identified in 60% (15/25 patients) of patients dying following ICU admission which was similar to the group of ICU survivors (57%; 39/67 patients). Most common identified bacterial pathogens were coagulase-negative staphylococci sp. (16%; 15/92 patients), enterococcus faecium (14%; 13/92 patients) and E. coli (21%; 19/92 patients).

In contrast, fungal infections were more likely in patients with fatal outcome after ICU admission (44%; 11/25 patients) than in the ICU survivor group (15%; 10/67 patients; *P* = .005) (**Supplementary Table S2**). Importantly, our institution started antifungal prophylaxis by posaconazole in 01/2012 for all AML patients receiving intensive chemotherapy. The effects of this paradigm shift were substantial (**Supplementary Table S3**). Fungal infections in AML patients needing ICU support dropped from 27% (16/59 patients) in the study period until 01/2012 to 15% (5/33 patients) since 01/2012, and we observed no disseminated fungal infections or fungemias in ICU admitted AML patients since then (2012-2017).

Leukemia-specific outcome

AML patients surviving ICU treatment received less cycles of chemotherapy (**Table 4)**. ICU survivors had to stop AML treatment more often already after one cycle of induction treatment (24%; 12/51 patients) than never-ICU patients (7%; 12/164 patients; *P* = .004). The difference for the second cycle was not significant (31% versus 24%). ICU survivors less often had the planned full program of two chemotherapy cycles and one consolidation treatment (45%; 23/51 patients versus 69%; 113/164 patients; *P* = .003).

The frequency of AML relapses was similar in ICU survivors (35%; 18/51 patients) and never-ICU patients (48%; 78/164), after a median follow-up in ICU survivors of 14.4 months and 20.3 months in never-ICU patients. The PFS was inferior for all patients needing ICU admission (median, 7.7 versus 15.5 months; *P* = .005) as was OS (median, 9.2 versus 30.0 months; *P* = .002; **Figure 3**). However, when comparing ICU surviving patients with never-ICU patients, differences for PFS (median, 22.3 versus 15.5 months) and for OS (median, 46.5 versus 30.0 months) were no longer significant.

DISCUSSION

Intensivists and oncologists face the dilemma of limited resources and, subsequently, must limit ICU admissions to cancer patients with a reasonable probability for recovery. Accordingly, previous studies have indicated that between 25 and 51% of all oncologic patients requiring ICU treatment are refused at admission [13,14]. Nevertheless, ICU survival rates are steadily improving for oncologic patients, and in-hospital survival rates have become similar to those of patients with other severe conditions such as heart disease or liver cirrhosis [11,15]. Consequently, refined predictors of ICU survival are an unmet need to characterize those oncologic patients that can benefit most from ICU care.

In this retrospective analysis of 240 consecutive AML patients receiving intensive chemotherapy with curative intent at a single academic center, roughly a third of patients (n=76; 32%) were admitted to a single tertiary medico-surgical ICU at least once during their planned three cycles of intensive AML treatment; finally, a third of these patients ultimately died following ICU admission (n=25/76; 33%). These survival rates appear comparable to previous studies of hemato-oncologic patients admitted to the ICU [16-22].

Our study aimed to identify factors associated with favorable outcome following ICU admissions. *NPM1* mutations were more common in the ICU survivor group (29%) as compared to patients with fatal outcome after ICU admission (8%). This observation raises the hypothesis that patients labeled as “good-risk” – such as AML patients with *NPM1* mutations – may have more favorable outcomes even in the case they need intensive care, whereas less favorable genetic AML subtypes have been reported as predictive of poor outcomes following ICU admission [17,18,22].

Our univariate analysis identified several therapeutic modalities associated with unfavorable outcome following ICU admission. Mechanical ventilation was needed in 100% of all ICU admissions with lethal outcome compared to 43% in the ICU survivor group ($P < .001$). This is consistent with a previous study in leukemia patients requiring invasive ventilation, in which intubation was associated with a 17% increase in mortality [23]. Moreover, invasive ventilation

is widely described as predictive of mortality in patients with hemato-oncologic malignancies [24-26]. In our study, patients needing invasive ventilation were less likely to survive to ICU discharge than those avoiding intubation. Other ICU treatment modalities associated with fatal ICU outcome were the need for catecholamine support, dialysis and automated external defibrillator.

Patients who died following ICU admission had significantly more often a septic condition. In accordance with this observation, other studies reported that hemato-oncologic patients with septic shock requiring ICU treatment have high mortality rates ranging from 47 to 60% [15,26-28]. Thus, while outcomes of hemato-oncologic patients with septic shock are improving [29], it appears that this population still has a high risk of mortality in the ICU. Remarkably, we observed no differences in incidence and types of bacterial pathogens isolated in AML patients with fatal outcome compared with ICU surviving patients. In contrast, fungal infections were more likely in patients with fatal outcome after ICU admission. Thus, an obviously important change during the study period at our institution was the introduction of anti-fungal prophylaxis with posaconazole to all AML patients receiving intensive chemotherapy. The effect of this paradigm shift was substantial, since fungal infections in AML patients needing ICU support dropped from 27% to 15%, and we observed no disseminated fungal infections or fungemias in ICU admitted AML patients since then. Thus, eliminating a single factor - such as disseminated fungal infections – had a significant effect on the survival probability of critically ill AML patients.

The strengths of this analysis comprise the extensive size of our AML-specific cohort compared to previous studies which assessed outcomes of mixed types of hemato-oncologic patients admitted to the ICU [9]. Limitation of our study was its single center design with no formal ICU admission criteria, potentially resulting in selection and time bias. In addition, quality of life (QOL) and functional status assessments were unavailable.

Finally, our analysis of a large cohort suggests that AML-specific outcome is similar between patients surviving ICU treatment and patients never needing ICU treatment during intensive chemotherapy. In particular, no differences for PFS and for OS were observed between ICU-

surviving AML patients and never-ICU patients. This finding is remarkable since we observed that AML patients surviving ICU treatment received less cycles of chemotherapy, most likely due to reduced general condition prohibiting further intensive treatment. Whereas larger series of patients may be needed to verify this observation, our data suggest that more AML patients undergoing intensive chemotherapy survive ICU treatment and that the long-term perspective of ICU surviving AML patients is comparable to that of AML patients never needing ICU treatment.

Finally, this analysis demonstrates that the outcomes of AML patients in need of intensive care have substantially improved over the last years. These results may encourage clinicians to consider ICU admission and intensive care treatment for critically ill AML patients during intensive chemotherapy, and they emphasize the need for facilitated access to intensive care for these patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORSHIP AND CONTRIBUTION

PF: performed research and analyzed data; BJ, UN: contributed vital material; YQ, SJ, BM, UB: contributed vital data; BG, OE: analyzed data; and TP: designed research and analyzed data. All authors participated in drafting or reviewing the report and all authors approved the submitted version.

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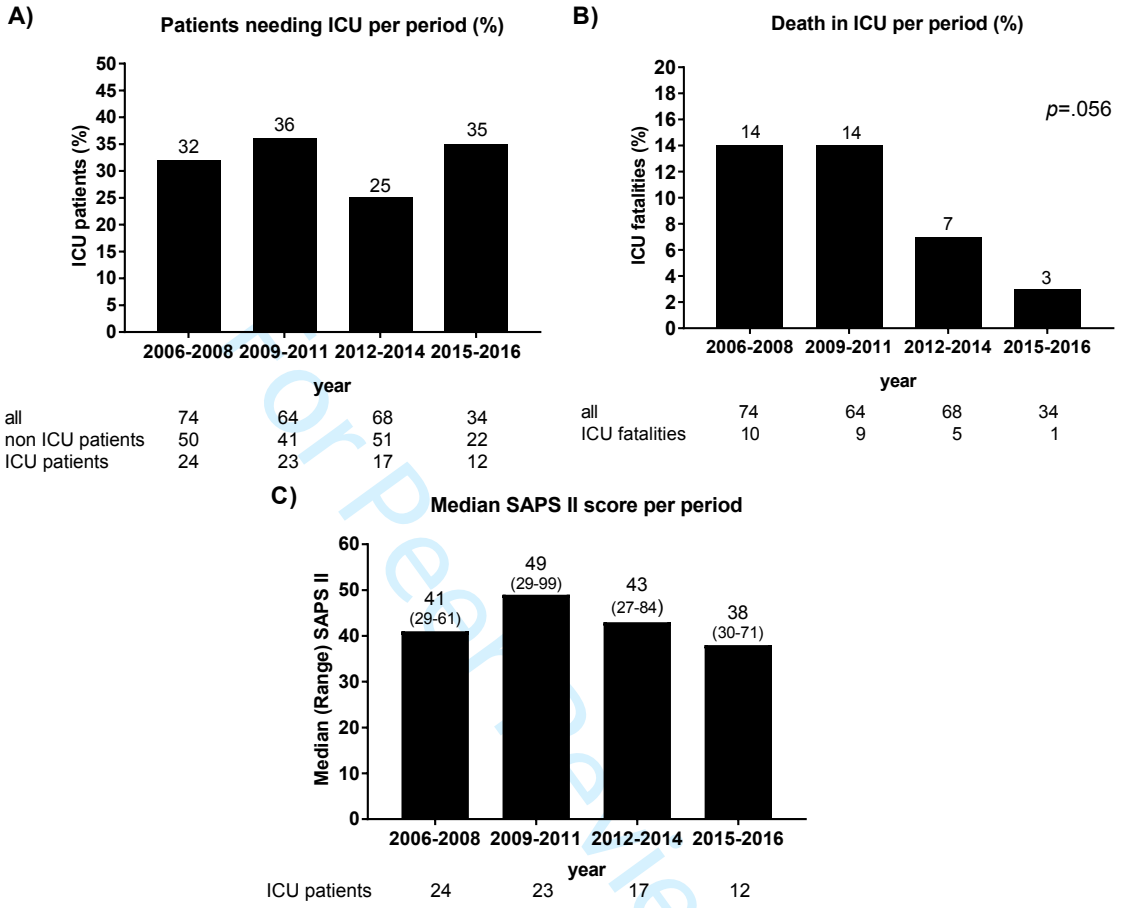
FIGURE LEGENDS

Figure 1: ICU admission rate, ICU mortality rate and SAPS II scores during the study period. (A) Depicted is the proportion of AML patients receiving intensive chemotherapy which were admitted to the ICU during the various periods of the study. (B) The mortality rate is shown of all patients receiving intensive chemotherapy during the study periods. (C) The median of SAPS II scores is demonstrated of all ICU patients during the various periods of the study.

Figure 2: Survival probability depending on duration and number of organ system failures during ICU. (A) The survival probability of AML patients is summarized admitted to the ICU depending on duration of ICU treatment. (B) The survival probability of AML patients admitted to the ICU is demonstrated depending on the number of failing organ systems.

Figure 3: Progression-free (PFS) and overall survival (OS). (A) PFS and (B) OS of AML patients never needing ICU treatment compared to patients needing ICU treatment at least once during intensive chemotherapy treatment. (C) PFS and (B) OS of AML patients surviving ICU treatment compared to patients never needing ICU treatment.

Figure 1



all	74	64	68	34
non ICU patients	50	41	51	22
ICU patients	24	23	17	12

all	74	64	68	34
ICU fatalities	10	9	5	1

ICU patients	24	23	17	12

Figure 2

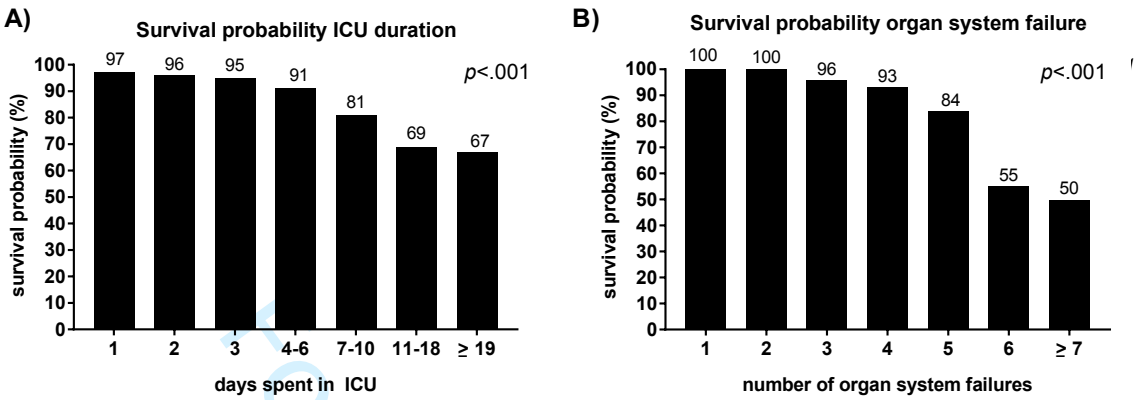


Figure 3

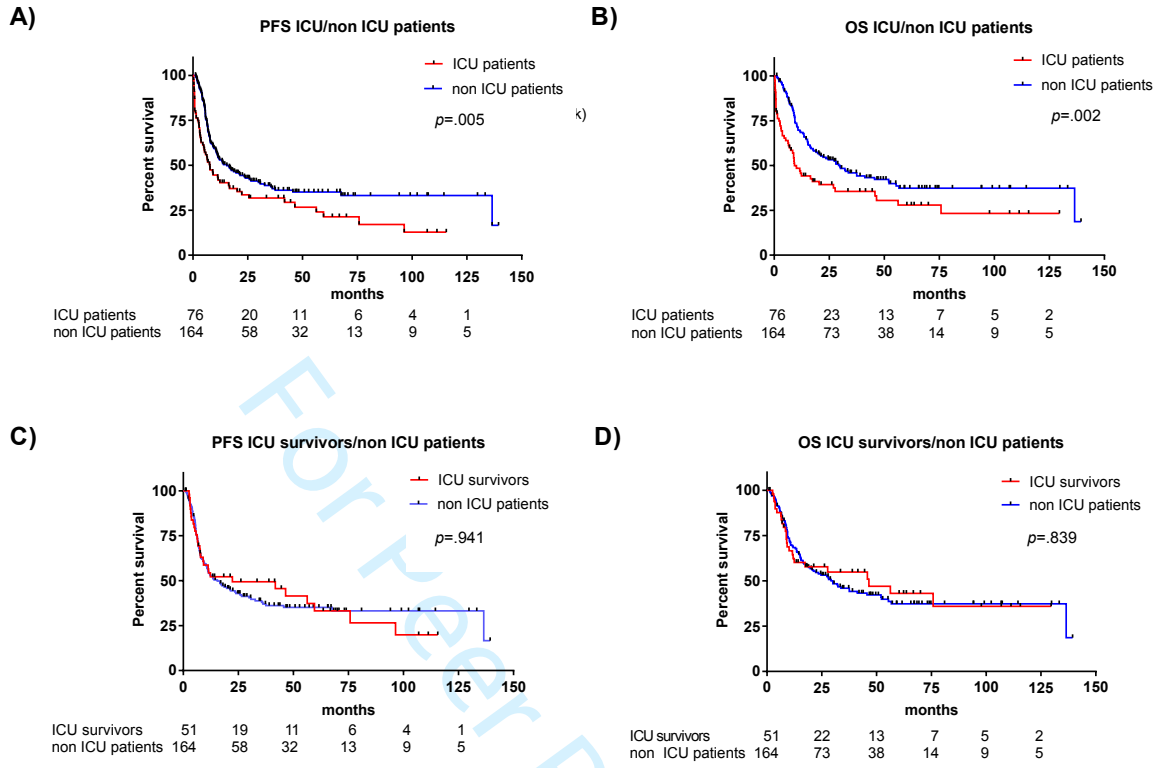


Table 1: Demographic features, laboratory parameters and characteristics of the AML in all patients admitted to ICU versus those that never require ICU care, and in patients with fatal outcomes versus those surviving the ICU period.

Parameter	all ICU patients (n=76)		never-ICU patients (n=164)		*p*	fatal ICU outcome (n=25)		ICU survivors (n=51)		*p*
Male/female, n	47/29		86/78		ns	19/6		28/23		ns
Age at diagnosis	57		57		ns	57		57		
ELN risk; favorable, n (%)	24	(32)	55	(33)	ns	7	(28)	17	(33)	ns
intermediate, n (%)	18	(24)	36	(22)	ns	6	(24)	12	(24)	ns
adverse, n (%)	32	(42)	70	(43)	ns	11	(44)	21	(41)	ns
ND, n (%)	2	(2)	3	(2)	ns	1	(4)	1	(2)	ns
Molecular mutations:										
CEBPA, n (%)	3	(4)	4	(2)	ns	0	(0)	3	(6)	ns
NPM1, n (%)	17	(22)	39	(24)	ns	2	(8)	15	(29)	.042
FLT3-ITD/-TKD, n (%)	13	(17)	36	(22)	ns	4	(16)	9	(18)	ns
WBC, G/L, median (range)	8.6	(0.4-575)	6.4	(0.5-270)	ns	13.4	(0.4-181)	8.2	(0.9-575)	ns
LDH, IU/L, median (range)	637	(213-2858)	697	(117-5154)	ns	632	273-2291	637	(213-2858)	ns
Bone marrow blasts, %, median	70		70		ns	70		70		ns
Peripheral blasts, %, median	25		33.5		ns	22.5		28.5		ns

ICU: intensive care unit; ELN: European Leukemia Net risk classification; ND: risk classification was not possible due to missing cytogenetic and/or molecular analysis; WBC: white blood cells; LDH: lactate dehydrogenase with upper normal level <480 IU/L; median values are given whereas not otherwise indicated.

Table 2: ICU admissions, organs systems involved and ICU interventions in patients with fatal outcomes versus patients surviving the ICU period.

Parameter	Deaths in ICU (n=25; 27.2%)	ICU survivors (n=67; 72.8%)	*p* values
ICU admission in cycle 1, n (%)	14 (56)	41 (61)	ns
cycle 2, n (%)	6 (24)	16 (24)	ns
cycle 3, n (%)	1 (4)	4 (6)	ns
re-induction, n (%)	4 (16)	6 (9)	ns
Mortality rate in cycle 1, n (%)	14/55 (26)		
cycle 2, n (%)	6/22 (27)		
cycle 3, n (%)	1/5 (20)		
re-induction, n (%)	4/10 (40)		
ICU admission, after onset of:			
chemotherapy, day, (range)	12 (4-23)	15 (1-69)	ns
neutropenia, day, (range)	11 (2-36)	11 (1-62)	ns
ICU duration, days, median (range)	6 (1-19)	3 (1-38)	ns
Failing organ systems:			
sepsis, n (%)	23 (92)	43 (64)	.009
renal, n (%)	14 (56)	20 (30)	.029
pulmonary, n (%)	24 (96)	38 (57)	<.001
cardiac, n (%)	23 (92)	40 (60)	.002
DIC, n (%)	6 (24)	10 (15)	Ns
CNS, n (%)	9 (36)	23 (34)	Ns
colitis, n (%)	13 (52)	24 (36)	Ns
paralytic ileus, n (%)	5 (20)	4 (6)	Ns
Bleeding, n (%)	13 (52)	22 (33)	Ns
hepatic, n (%)	5 (20)	6 (9)	Ns
Number of failing organ systems, (range)	5 (3-9)	3 (1-8)	<.001
Interventions during ICU stay:			
mechanical ventilation , n (%)	25 (100)	29 (43)	<.001
duration, days, (range)	4 (1-16)	3 (3-34)	ns
catecholamines, n (%)	24 (96)	24 (36)	<.001
antibiotics, n (%)	25 (100)	67 (100)	ns
dialysis, n (%)	9 (36)	6 (9)	.004
AED, n (%)	4 (16)	2 (3)	.044
Patients with failing organ systems:			
1 system, n (%)	0 (0)	9 (13)	Ns
2 systems, n (%)	0 (0)	11 (16)	.032
3 systems, n (%)	3 (16)	16 (24)	.022
4 systems, n (%)	4 (16)	18 (27)	.004
5 systems, n (%)	6 (24)	4 (6)	Ns
6 systems, n (%)	9 (36)	6 (9)	Ns
7 systems, n (%)	0 (0)	2 (3)	Ns
8 systems, n (%)	1 (4)	1 (2)	Ns
9 systems, n (%)	2 (8)	0 (0)	Ns

ICU: intensive care unit; median values are given whereas not otherwise indicated; bleeding events comprised: intestinal: 6 (24%) vs 14 (21%); intracranial: 3 (12%) vs 4 (6%), pulmonary: 4 (16%) vs 1 (2%; *p*=0.0183); others 1 (4%) vs 3 (5%); DIC: disseminated coagulopathy; dialysis: extrarenal therapy; CNS: central nervous system; AED: automated external defibrillator.

Table 3: Multivariable predictors of disease progression and of death.

	Disease Progression		Death	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Full model				
ICU	1.81 (1.12 to 2.92)	0.015	2.68 (1.64 to 4.37)	<0.001
Year (centered, per year)	0.90 (0.84 to 0.96)	0.002	0.85 (0.79 to 0.92)	<0.001
ICU x year	1.06 (0.91 to 1.23)	0.452	1.17 (1.00 to 1.38)	0.051
Age (per 10 years)	1.18 (1.03 to 1.36)	0.021	1.22 (1.04 to 1.42)	0.012
ELN risk	1.64 (1.35 to 2.00)	<0.001	1.69 (1.37 to 2.08)	<0.001
Antifungal prophylaxis	0.99 (0.41 to 2.35)	0.973	0.82 (0.32 to 2.09)	0.683
Specific contrasts				
Effect of ICU in 2006	1.36 (0.73 to 2.52)	0.336	1.21 (0.64 to 2.29)	0.564
Effect of ICU in 2011	1.81 (1.12 to 2.92)	0.015	2.68 (1.64 to 4.37)	<0.001
Effect of ICU in 2016	2.41 (0.81 to 7.23)	0.116	5.93 (1.85 to 18.96)	0.003
Effect of year in patients not admitted to ICU	0.90 (0.84 to 0.96)	0.002	0.85 (0.79 to 0.92)	<0.001
Effect of year in patients admitted to ICU	0.95 (0.83 to 1.10)	0.493	1.00 (0.86 to 1.15)	0.967

ICU, intensive care unit. ELN, European Leukemia Net.

Table 4: AML treatments and clinical outcomes in ICU survivors versus patients never needing ICU care.

Parameter	ICU survivors (n=51)		never-ICU (n=164)		*p* values
Only one induction cycle received, n (%)	12	(24)	12	(7)	.004
Two induction cycles received, n (%)	16	(31)	39	(24)	Ns
Three cycles including consolidation with: n (%)	23	(45)	113	(69)	.003
conventional chemotherapy, n (%)	3	(6)	18	(11)	ns
autologous transplantation, n (%)	17	(33)	79	(48)	ns
allogeneic transplantation, n (%)	3	(6)	16	(10)	ns
Relapse, n (%)	18	(35)	78	(48)	ns
time since diagnosis, in days, median (range)	233	(86-2895)	231	(64-2031)	ns
Mortalities, n (%)	25	(49)	91	(56)	ns
Median follow up; months (range)	14.4	(1.4-127.8)	20.3	(1.3-138)	ns
5 year PFS, n (%)	9	(18)	25	(15)	ns
5 year OS, n (%)	11	(22)	27	(17)	ns

ICU: intensive care unit; median values are given whereas not otherwise indicated; PFS: progression-free survival; OS: overall survival.

Supplementary Table S1: Cytogenetic abnormalities and FAB subtypes at diagnosis of AML.

Parameter	all ICU patients (n=76)	never-ICU (n=164)	*p* values	fatal ICU outcome (n=25)	ICU survivors (n=51)	*p* values
Cytogenetic abnormalities:						
t(15;17), n (%)	4 (5)	8 (5)	ns	3 (12)	1 (2)	ns
t(8/21), n (%)	5 (7)	13 (8)	ns	2 (8)	3 (6)	ns
inv(16), n (%)	3 (4)	6 (4)	ns	2 (8)	1 (2)	ns
trisomy 11, n (%)	1 (1)	2 (1)	ns	0 (0)	1 (2)	ns
deletion 7, n (%)	9 (12)	13 (8)	ns	2 (8)	7 (14)	ns
trisomy 8, n (%)	7 (9)	9 (6)	ns	0 (0)	7 (14)	ns
AML (FAB) classification:						
M0, n (%)	12 (16)	23 (13)	ns	4 (16)	8 (16)	ns
M1, n (%)	15 (20)	27 (17)	ns	3 (12)	12 (22)	ns
M2, n (%)	20 (26)	41 (25)	ns	6 (24)	14 (28)	ns
M3, n (%)	4 (5)	9 (6)	ns	3 (12)	1 (2)	ns
M4, n (%)	9 (12)	22 (13)	ns	5 (20)	4 (8)	ns
M5, n (%)	6 (8)	23 (14)	ns	1 (4)	5 (10)	ns
M6, n (%)	1 (1)	7 (4)	ns	0 (0)	1 (2)	ns
M7, n (%)	0 (0)	1 (1)	ns	0 (0)	0 (0)	ns
ND, n (%)	9 (12)	11 (7)	ns	3 (12)	6 (12)	ns

ICU: intensive care unit; FAB: French-American-British classification; ND: FAB classification not possible.

Supplementary Table S2: Infectious pathogens identified in ICU patients.

Parameter	fatal ICU outcome (n=25)	ICU survivors (n=67)	*p* values
Fungal infections, n (%)	11 (44)	10 (15)	.005
Candida albicans, n (%)	5 (20)	2 (3)	.014
other Candida (lusitaniae, dubliniensis), n (%)	2 (8)	0 (0)	ns
Aspergillus spp., n (%)	2 (8)	3 (4)	ns
others (yeast, mould), n (%)	4 (16)	0 (0)	.004
ND fungal infections (CT), n (%)	2 (8)	5 (7)	ns
Bacterial infections, n (%)	15 (60)	39 (57)	ns
Bacillus cereus, n (%)	1 (4)	3 (4)	ns
Pseudomonas aeruginosa, n (%)	1 (4)	2 (3)	ns
Pseudomonas spp, n (%)	1 (4)	0 (0)	ns
MRSA (staphylococcus aureus), n (%)	0 (0)	3 (4)	ns
Enterococcus faecium, n (%)	5 (20)	8 (12)	ns
other Enterococcus spp, n (%)	0 (0)	1 (2)	ns
Enterobacter cloacae, n (%)	2 (8)	1 (2)	ns
Staphylococcus coagulase-negative (SCN), n (%)	3 (12)	12 (18)	ns
E. coli, n (%)	3 (12)	16 (24)	ns
Klebsiella pneumoniae, n (%)	1 (4)	4 (6)	ns
Klebsiella oxytoca, n (%)	1 (4)	3 (4)	ns
Clostridium difficile (fecal positive), n (%)	2 (8)	2 (3)	ns
others *, n (%)	1 (4)	9 (13)	ns

*others: Streptococcus viridans (n=4); Bacillus thuringiensis (n=2); Mycobacterium spp. (n=1); Stenotrophomonas maltophilia (n=1); Citrobacter sp (n=1); Cocci sp. ND (n=1); multiple infections can be listed in single patients; ND: not determined; ICU: intensive care unit.

Supplementary Table S3: Fungal infections depending on study period.

Parameter	no posaconazole prophylaxis <2012; n=59	with posaconazole prophylaxis ≥2012; n=33	*P* values
Fungal infections: total, n (%)	16/59 (27)	5/33 (15)	ns
in ICU patients with fatal outcome, n (%)	11/21	0/4	ns
in patients surviving ICU admissions, n (%)	5/38	5/29	ns
Disseminated fungal infections/fungemia:			
in ICU patients with fatal outcome, n (%)	4	0	ns
in patients surviving ICU admissions, n (%)	4	0	ns

ICU: intensive care unit; ns: not significant.

Supplementary Table S4: Definitions of failing organ systems as used in this analysis.

Failing organ system	
sepsis	2 out of the 4 following points: 1. temperature > 38.0°C or < 36.0°C 2. respiratory rate > 20/min or $PaCO_2$ < 32 mmHg (< 4.3 kPa) 3. heart rate > 90/min 4. white blood cell (WBC) count > 12 G/L, < 3 G/L, or > 10% immature neutrophils qSOFA: 2 of the following points: - respiratory rate ≥ 22/min - GCS >15 - systolic BP ≤ 100 mmHg
renal	- increase in the serum creatinine value of 0.3 mg/dl within 48 hours - or a 1.5-1.9-fold increase of the serum creatinine value within 7 days - or an urine production of < 0.5 ml/kg body weight/h during 6 hours
pulmonary	arterial blood gas analysis: - pO2 < 72 mmHg - oxygen saturation < 90% - pCO2 > 46 mmHg - reduced Horovitz-Quotient :PaO2/FiO2 < 200 mmHg
cardiac	- BP systolic < 90 mmHg (or < 30mmHg to prior BP) - Cardiac index < 2.1ml/min /m^2 Echocardiography: - LVEF <30% - high cardiac filling pressure (PCWP >16 mmHg or/and RAP >12 mmHg) Laboratory: - BNP >100 pg/ml
DIC	Laboratory abnormalities: - prolonged INR (> 1) / aPTT (> 36 sec) - decrease in the platelet count (<100`000/µl) - decrease in fibrinogen (<100mg/dl) - increase of d-dimer (>500 µg/l)
CNS	Glasgow coma scale <15 points
colitis	Ultrasound examination or X-ray: - thickening small bowel > 3 mm/ colonic wall > 2-5 mm - dilation of the intestinal loops
paralytic ileus	Clinically are no rumors heard for over three minutes, or flatus or stool are absent
bleeding	Symptoms: -hypotension > 100/60 mmHg - heart rate < 100 per minute - or disturbance of consciousness - melena Ultrasound: - free liquid Laboratory: - erythrocytes: men < 4,8-5,9 Mio./µl; women < 4,3-5,2 Mio./µl - hemoglobin concentration: men<13-18 g/dl; women:<12-16 g/dl
hepatic	laboratory: - INR > 1.5, - total bilirubin > 2 mg/dl - serum creatinine > 1.4 mg/dl - serum albumin < 3.5 g/dl Sonography: ascites

BP: blood pressure; qSOFA: quick sepsis-related organ failure assessment score; pO2 oxygen partial pressure; pCO2: carbon dioxide partial pressure; LVEF: left ventricle ejection fraction; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure; BNP: brain natriuretic peptide; peak; DIC: disseminated intravascular coagulation; INR: international normalized ratio; aPTT: activated Partial Thromboplastin Time; CNS: central nervous system.